Impact of Clinical Outcome Measures on Placebo Response Rates in Clinical Trials for Chronic Constipation: A Systematic Review and Meta-analysis

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OBJECTIVES: **Chronic constipation (CC) is a recurrent functional bowel disorder worldwide. The purpose of this study is to examine its pooled placebo response rate and compare placebo response level in randomized controlled trials (RCTs) with different endpoint assessments.**

METHODS: **PubMed, Cochrane Library, and Embase were electronically searched for therapeutic RCTs of CC with placebo control. Data extraction and assessment of risk of bias were performed independently by 2 reviewers. All the statistical calculation and analysis were performed using R 3.6.0. Our protocol has registered in PROSPERO with registration number: CRD42019121287.**

RESULTS: **There were 46 studies included with 5,992 constipated patients allocated to the placebo arm in total. The pooled placebo response rate was 28.75% (95% confidence interval: 23.83%–33.67%) with significant heterogeneity among trials (I^2 = 93.6%). Treatment efficacy assessed using subjective improvement had a significantly higher placebo response rate than that assessed with improvement in complete (spontaneous) bowel movements or composite improvement (41.40% vs 18.31% or 20.35%, P < 0.001). According to the results of meta-regression, active treatment and endpoint assessment were most likely to lead to the huge heterogeneity among studies.**

DISCUSSION: **Patients with CC have significant response level to placebo. Based on findings in this study, we do not recommend subjective improvement as endpoint while designing therapeutic RCTs for chronic constipated patients.**

SUPPLEMENTARY MATERIAL accompanies this paper at https://links.lww.com/CTG/A413, https://links.lww.com/CTG/A414, https://links.lww.com/CTG/A415, https://links.lww.com/CTG/A416, https://links.lww.com/CTG/A417.

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INTRODUCTION

Chronic constipation (CC) is a recurrent functional bowel disease with a global prevalence rate at about 14% (1–5). Although not life-threatening, it could lead to a decline in the quality of life for patients and a heavy burden on the health service system (3,6,7). A large number of clinical trials has been performed recent years, but the effect is still not satisfactory (1,3,8–10). Therefore, further exploration of new treatment methods is still necessary.

Although many of the RCTs use placebo as a comparator to detect the medication effect of active drugs, the medication response cannot be simply calculated by the sum of placebo response and medication effect (11,12). Whatever the real relationship between medication response and placebo response is, there is possibility to make wrong conclusion on the true medication effect when compared with placebo in clinical trials. Moreover, high placebo response adds to the difficulty to prove the effect of a therapeutic drug, leading to the further time-consuming and expensive multicenter clinical trials to obtain reliable result with a larger sample size (12,13). Taking this 2 RCTs conducted by Ziegenhagen et al. (14) and Harish et al. (15), e.g., both of which failed to detect the statistical difference between the treatment group and control group. Both authors discussed in their articles that this result may due to the limitation of small sample size. As a result, it is the consensus to minimize placebo response in clinical trials and maximize it during clinical practice (12,13,16). However, no literature has reported that the placebo response rate in patients with CC ranges from 7% to 75% (4,17–20).

Previous meta-analysis reported the placebo response rate in chronic idiopathic constipation with outcome of CSBM (21), but they did not notice that a considerable number of RCTs used

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subjective improvement evaluated by patients as efficacy assessment. Therefore, we conduct this systematic review and meta-analysis to update the pooled placebo response rate in constipated patients and its related factors, as well as compare the placebo response level in RCTs with different efficacy assessments. This study has been registered with ID number CRD42019121287 on the PROSPERO International Prospective Register of systematic reviews. And, the study protocol has been published online (DOI: 10.1097/MD.0000000000019020).

METHODS

Search strategy and eligibility assessment

PubMed, Cochrane Library, and Embase were electronically searched from their inception to March 1, 2019, with no restriction of publication dates and languages. The search strategy includes the medical subject headings terms and the keywords that describe the intervention (placebo and sham stimulation), the characteristic of participants (CC, functional constipation, and irritable bowel syndrome with predominant constipation [IBS-C]), and RCTs. The full electronic search strategy can be seen in text (see Supplemental Digital Content 1, http://links.lww.com/CTG/A413).

All the studies obtained from databases were assessed according to the inclusive criteria (Table 1). The studies were excluded if the constipation of participants was induced by drugs, organic diseases related to digestive tract, or other systemic diseases based on obvious and definite evidence, e.g., the result of an endoscopy, biopsy, and laboratory tests.

Table 1. Inclusive criteria

Randomized controlled trials or crossover designed
Adults (participants older than 16 yr)
Diagnosis of chronic constipation, functional constipation, or IBS-C based on Rome III criteria.
Compared pharmacological therapies (psyllium, PEG, chloride channel activators lubiprostone, guanylate cyclase C agonists linaclotide, prucalopride, etc.) with placebo, or compared electroacupuncture and acupuncture therapies with sham stimulation.
Minimum duration of therapy: 7 d
Placebo response rate after therapy on improvement of constipation symptoms (frequency of bowel movements, stool consistency, etc.) or subjective improvement questions answered by patients.
IBS-C, irritable bowel syndrome with predominant constipation; PEG, polyethylene glycol.

Outcomes of interest

The outcome assessment was made according to patient-reported information or using questionnaires based on Rome III which designed at the beginning of every RCTs. The primary outcome is the placebo response rate of subjective improvement or composite improvement over constipation symptoms or based on Patients Assessment on Constipation Symptoms and Patients Assessment of Constipation Quality of Life scores. The subjective improvement is defined as patients assessed themselves as satisfactory remission using a single question as "How do you assess your relief of constipation symptoms?" or "Have you had adequate relief of constipation symptoms?" The composite improvement is defined as patients who experienced 2 or more aspects of the following symptoms: improvement in bowel movement (spontaneous bowel movements, CSBM, etc.), reduced frequency of hard or lumpy stools, reduced frequency of straining, improvement of the sense of incomplete evacuation, improvement of the feeling of anorectal blockage, decrease of the need for digital manoeuvres to assist defecation, and improvement in abdominal pain (for IBS-C only). The additional outcome is the placebo response rate for one of the above bowl symptom improvements.

Records retrieve and data extraction

The records retrieve was conducted independently by 2 reviewers (J.C. and X.L.) according to the Cochrane Handbook. Then, these 2 reviewers independently screened both titles and abstracts for eligibility based on the inclusive and exclusive criteria described above. The records management was performed using EndNote X9.

Full texts of each eligible articles were viewed, and the related data were extracted by 2 reviewers (J.C. and X.L.) independently. Risk of bias for clinical trials was assessed using Cochrane risk-of-bias tool by 2 reviewers (J.C. and X.L.) independently. Risk-of-bias graph and risk-of-bias summary were performed in RevMan 5.4. Any differences emerged during this procedure were discussed by the 2 reviewers (J.C. and X.L.). If no consensus was reached, then an independent reviewer (T.B.) was consulted for further solution. The data needed to be extracted include year of publication, geographical location, number of centers, active treatment, duration of therapy, dosing schedule, sample size, and placebo response rate (%).

Manuscripts from publishers, supplementary documents, and corresponding records with NCT numbers on ClinicalTrials.gov were retrieved for original data, when the experimental data were found to be inadequate or missing. Inadequate data were excluded if sufficient data could not be retrieved.

Data synthesis and statistical analysis

R 3.6.0 (https://www.r-project.org/) was used to calculate the pooled placebo response rate as well as its 95% confidence interval, draw the forest plot, and perform all the statistical analyses. The heterogeneity among all the included studies was assessed using I^2. Contour-enhanced funnel plot with and without moderators was drawn to evaluate the publication bias (22,23). After that, the method of trim and fill was performed to modify the asymmetry of funnel plot. The Egger test was conducted to provide more accurate evidence for publication bias. Subgroup analysis and meta-regression were performed to seek the potential reason that may cause significant heterogeneity. And, sensitivity analysis was conducted to test the stability of the results. Finally, the Grading of Recommendations, Assessment, Development, and Evaluation (24) was used to evaluate the cumulative evidence independently by 2 reviewers (J.C. and X.L.).

The ethics approval is not required for a systematic review and meta-analysis since this type of study use only the data from already published or unpublished but declared studies and does not have patient personal information.

RESULTS

We have retrieved 17,212 articles in total, and the full texts of 388 were screened. Forty-six studies with 5,992 constipated patients allocated to the placebo arm were included finally. The detail information about this procedure is summarized in the form of a

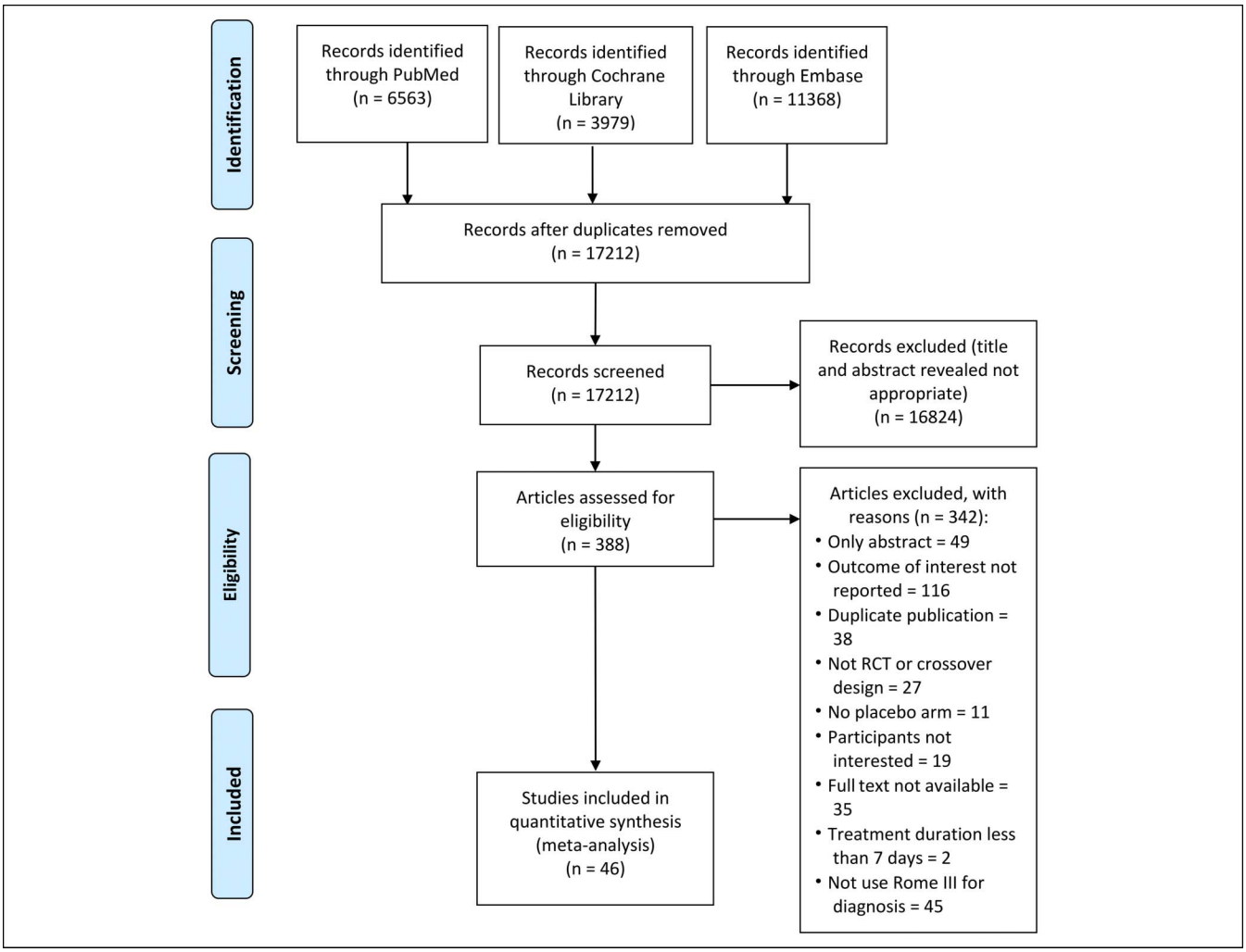

Figure 1. PRISMA flow diagram of inclusion of trials. PRISMA, preferred reporting items for systematic review and meta-analysis; RCT, randomized controlled trial.

preferred reporting items for systematic review and meta-analysis flow diagram (Figure 1). Risk-of-bias graph (Figure 2) and risk-of-bias summary (see Figure, Supplemental Digital Content 2, http://links.lww.com/CTG/A414) were performed to evaluate 7 risk-of-bias parameters for the whole and each study. And, there is no serious risk of bias in most studies.

Pooled placebo response rate

The pooled placebo response rate was 28.75% (95% confidence interval: 23.83–33.67%) with significant heterogeneity among trials ($I^2 = 93.6\%$, $P < 0.001$), using a random effects model. The individual placebo response rate of each studies varied from 5% to 71%. Forest plot for pooled analysis can be seen in (see Figure,

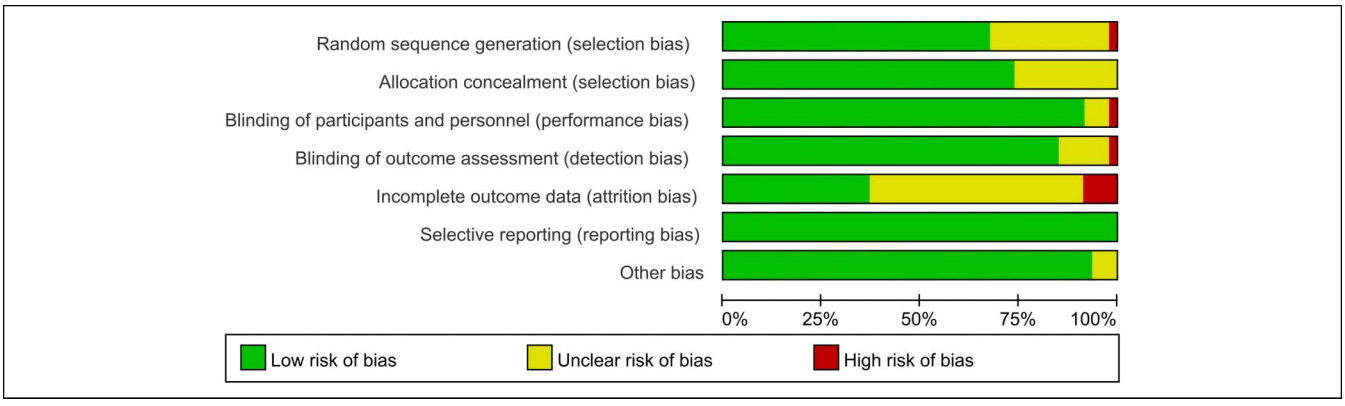

Figure 2. Risk-of-bias graph.

Table 2. Effect of trial characteristics on magnitude of the placebo response

	No. of trials	No. of patients receiving placebo	Pooled placebo response rate (%)	95% C	I^2 (%)	*P* value for I^2
All trials[a]	46	5,992	28.75	23.83–33.67	93.6	<0 .001 ***
Year of publication						
Before 2015	19	1,311	28.22	21.83–34.61	87.2	<0.001 ***
2015 or later	27	4,681	28.92	21.81–36.03	95.3	<0.001 ***
Trial location						
Europe	11	1,050	34.56	23.90–45.22	93.1	<0.001 ***
Oceania	1	64	43.75	31.60–55.90	—	—
Asia	20	1842	29.55	22.51–36.58	90.3	<0.001 ***
South America	2	53	29.11	0.00–59.08	78.9	0.03 *
North America	11	2,561	21.11	11.10–31.12	92.6	<0.001 ***
International	1	422	21.33	17.42–25.24	—	—
No. of centers						
Single center	7	249	32.34	20.87–43.82	83.4	<0.001 ***
Multicenter	29	5,165	24.85	19.33–30.36	92.1	<0.001 ***
Not stated	10	578	38.27	25.51–51.04	92.8	<0.001 ***
Diagnosis of participants						
IBS-C	9	1754	22.76	16.97–28.56	77.1	<0.01 **
FC	21	2,360	32.91	24.20–41.61	94.7	<0.001 ***
FC and IBS-C	3	217	36.17	10.19–62.16	94.6	<0.001 ***
CC	13	1,661	23.35	16.58–30.12	92.1	<0.001 ***
Duration of therapy						
1–4 wk	25	1,671	34.21	27.03–41.38	92.0	<0.001 ***
5–8 wk	7	873	31.75	18.39–45.11	93.4	<0.001 ***
9–12 wk	14	3,448	17.43	13.32–21.53	90.1	<0.001 ***
Study design						
RCT	45	5,980	28.70	23.71–33.69	93.8	<0.001 ***
Crossover	1	12	33.33	6.66–60.01	—	—
Proportion of trial patients assigned to placebo						
Approximately 50%	29	2,940	29.20	23.99–34.41	88.9	<0.001 ***
Significantly less than 50%	17	3,052	27.81	17.77–37.85	95.8	<0.001 ***
Dosing schedule						
q.d.	26	3,908	30.31	23.00–37.62	94.1	<0.001 ***
b.i.d.	14	810	30.19	23.54–36.84	81.5	<0.001 ***
t.i.d.	1	20	50.00	28.09–71.91	—	—
Less than 1 time per d[a]	2	581	19.86	2.26–37.47	84.5	<0.001 ***
Not stated	3	673	8.81	3.16–14.46	78.8	<0.001 ***
Active treatment[b]						
Secretagogues	13	3,321	16.49	12.33–20.65	90.2	<0.001 ***
Serotonergic enterokinetic agents	3	298	23.42	1.44–45.40	86.2	<0.001 ***
Laxatives	5	429	34.48	13.71–55.24	94.2	<0.001 ***
Dietary supplement	9	410	46.48	34.42–58.54	88.4	<0.001 ***
Alternative treatment	9	958	29.18	18.64–39.72	91.7	<0.001 ***

Table 2. (*continued*)

	No. of trials	No. of patients receiving placebo	Pooled placebo response rate (%)	95% C	I^2 (%)	*P* value for I^2
Others	7	576	28.17	24.34–32.01	0.0	0.43
Endpoint assessment						
Subjective improvement	16	1,246	41.40	31.65–51.15	94.4	<0.001 ***
Composite improvement	9	1,545	20.35	16.77–23.93	62.1	<0.01 **
CSBM/CBM	17	3,027	18.31	13.38–23.23	88.6	<0.001 ***
PAC−SYM scores	1	41	43.90	28.71–59.09	—	—
Improvement in stool consistency	3	133	35.12	27.04–43.20	0.0	0.61

CC, chronic constipation; CI, confidence interval; CSBM/CBM, complete (spontaneous) bowel movement; FC, functional constipation; IBS-C, irritable bowel syndrome with predominant constipation; PAC−SYM, Patients Assessment on Constipation Symptoms; PEG, polyethylene glycol; RCT, randomized controlled trial; SNS, sacral nerve stimulation; SPS, sodium picosulfate.

[a]Two studies using electroacupuncture assigned the treatment as "5 sessions in each of the first 2 weeks, and 3 sessions in each of the remaining 6 weeks".

[b]Active treatment: secretagogues: linaclotide, plecanatide, lubiprostone, etc. Serotonergic enterokinetic agents: prucalopride, renzapride, cisapride, tegaserod, velusetrag, etc. Laxatives: PEG, bisacodyl, SPS, PMF-100, etc. Dietary supplement: fiber, probiotics, symbiotic, etc. Alternative treatment: herbal medicine, electrical stimulation such as SNS, etc. Others: CO2-releasing suppository, neurotrophin-3, mineral water, and other treatment that cannot be classified using above categories.

Supplemental Digital Content 3, http://links.lww.com/CTG/A415).

Subgroup analysis

Subgroup analysis was conducted according to different study characteristics extracted from included trials. Detail information of different trials can be seen in Table (see Supplemental Digital Content 4, http://links.lww.com/CTG/A416. And, all the results of subgroup analysis are contained in Table 2.

The placebo response rate in studies published before 2015 had no significant difference compared with studies published at 2015 and later (28.22% vs 28.92%, $P = 0.886$). Trials performed in North America had the minimum placebo response rate (21.11%), while trials performed in Europe had the second highest placebo response rate (34.56%, only lower than that in Oceania, which had only 1 study included in this meta-analysis). But, there was no statistical significance detected between these 2 locations ($P = 0.071$). Studies conducted in single center had a higher placebo response rate than that in studies conducted in multicenter, but without statistical difference (32.34% vs 24.85%, $P = 0.249$).

The higher placebo response rate occurred when patients assigned to active treatment and placebo at a ratio of 1:1 than others with no statistical difference (29.20% vs 27.81%, $P = 0.809$). Patients responded to placebo at equal level when the treatment was given once or twice a day (30.31% vs 30.19%, $P = 0.982$). The placebo response rate declined a lot when the therapy was given for 9–12 weeks compared with that for 5–8 weeks or 1–4 weeks (17.43% vs 31.75% or 34.21%, $P = 0.045$ and $P < 0.001$, respectively). The placebo response rates in patients diagnosed with functional constipation were higher than that in patients diagnosed with IBS-C without significant difference (32.91% vs 22.76%, $P = 0.057$).

Studies using secretagogues (guanylate cyclase C agonists and chloride channel activators) as active treatment were observed to have the lowest placebo response rate (16.49%) with statistical significance compared with studies using alternative treatment (herbal medicine and electrical stimulation) (29.18%), dietary supplement (fiber, probiotic, and symbiotic) (46.48%), and other treatment (28.17%) ($P = 0.028$, $P < 0.001$, and $P < 0.001$, respectively). However, the highest placebo response rate was observed in studies of dietary supplement, compared with studies of secretagogues, alternative treatment, and other treatment ($P < 0.001$, $P = 0.034$, and $P = 0.005$, respectively).

Treatment efficacy assessed using subjective improvement could significantly elevate the placebo response rate (41.40% vs 18.31% for improvement in complete (spontaneous) bowel movement (CSBM/CBM), $P < 0.001$ and 41.40% vs 20.35% for composite improvement, $P < 0.001$) (Figure 3). The placebo response rates were significantly lower with composite improvement and improvement in CSBM/CBM (20.35% vs 18.31%, $P = 0.510$) than that in any other endpoint assessment ($P < 0.01$).

Meta-regression and sensitivity analysis

Meta-regressions were performed according to different covariates describing different study characteristics. And, there were 2 main factors contributing to the great heterogeneity among studies: active treatment ($R^2 = 33.11\%$) and endpoint assessment ($R^2 = 34.22\%$). And, these 2 covariates together could explain 65.81% of the heterogeneity.

Then sensitivity analysis (see Figure, Supplemental Digital Content 5, http://links.lww.com/CTG/A417) showed that the random exclusion of any study did not lead to a significant change in the pooled placebo response rate, indicating the stability of the results.

Contour-enhanced funnel plot and publication bias

Contour-enhanced funnel plot without moderators showed asymmetry (Figure 4a), and the Egger test confirmed asymmetry ($P < 0.001$). The result of trim and fill for funnel plot showed that the estimated number of missing studies on the right side was 3 (Figure 4b). Then contour-enhanced funnel plot with moderators (active treatment and endpoint assessment) was performed, with an insignificant $P = 0.075$ for the Egger test (Figure 4c).

Summary of finding

The quality of evidence for different outcomes was displayed in summary of finding table using Grading of Recommendations, Assessment, Development, and Evaluation according to Cochrane recommendation (Table 3). And, most of them had a moderate grade for quality of evidence.

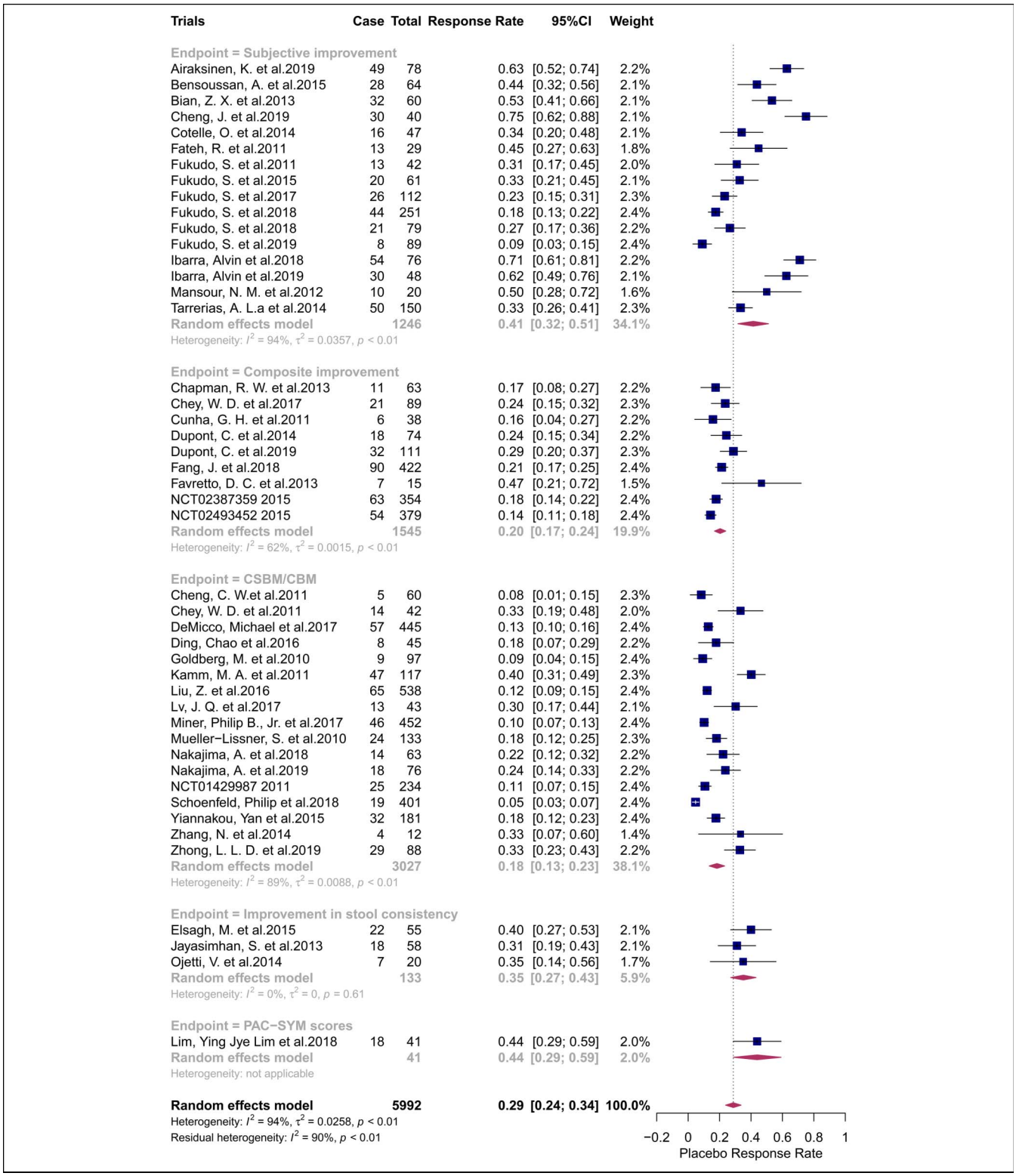

Figure 3. Forest plots with subgroup of different endpoint assessment. CI, confidence interval; CSBM/CBM, complete (spontaneous) bowel movement.

DISCUSSION

Patients with CC had a significant placebo response rate at around 30%, which varied with different factors. According to the results of meta-regression, active treatment and endpoint assessment were most likely to lead to the huge heterogeneity among studies.

Placebo response is defined as any improvement after a period of inactive treatment, which is caused by patient expectations and other different factors (16,25). Previous study showed that more follow-up visits in clinical trials lead to higher placebo response (26) because more frequent contact related to therapy can

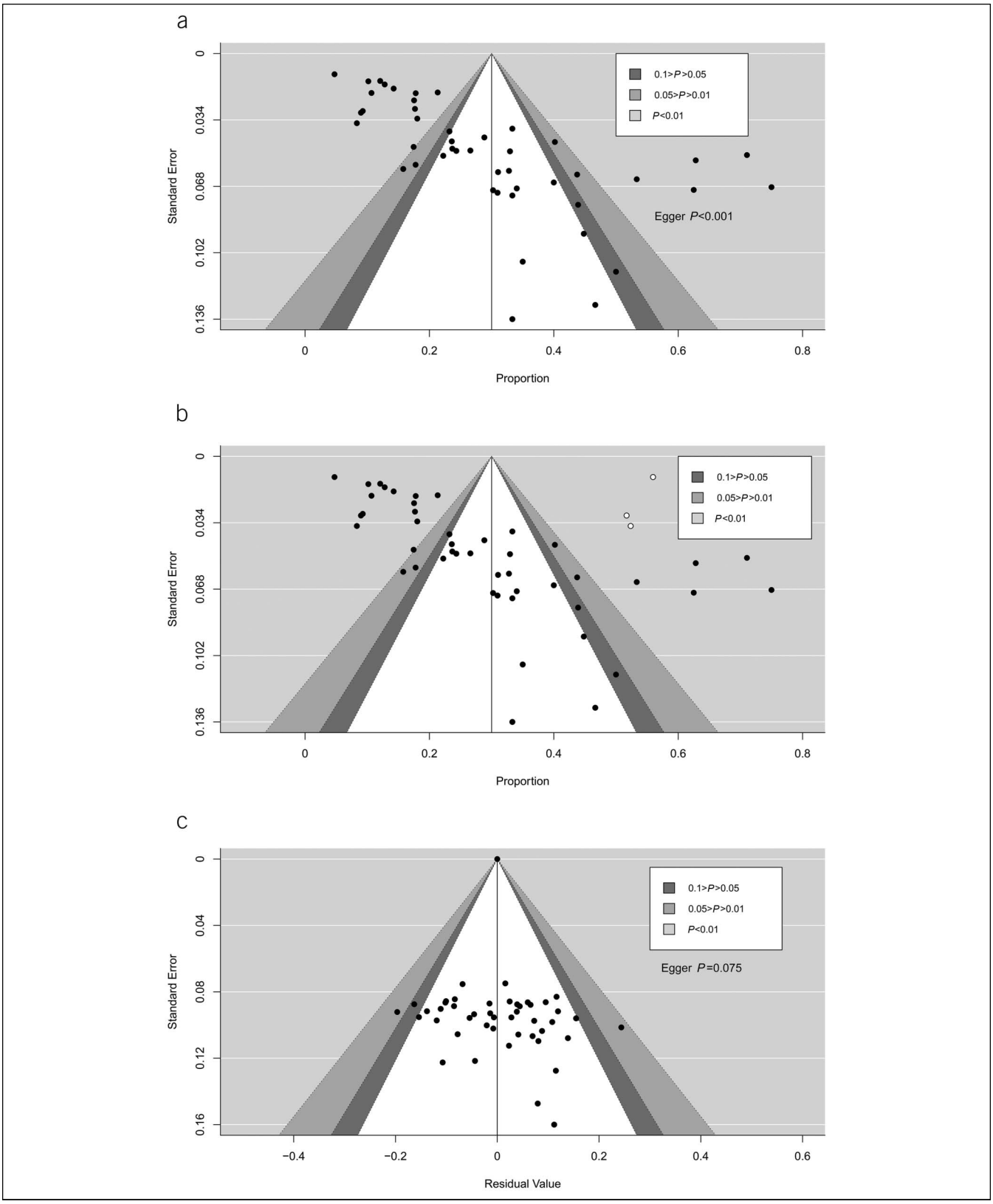

Figure 4. Contour-enhanced funnel plot without moderators (**a**), with trim and fill (**b**), and with moderators (active treatment and endpoint assessment) (**c**).

reinforce the patient expectation of symptom remission (13). However, there was no difference on the placebo response rate between treatment given once a day and twice a day in this meta-analysis. Although there was a tendency that treatment given less than 1 time per day leads to lower placebo response and treatment given 3 times per day leads to higher placebo response, these

Table 3. Summary of findings (GRADE evidence profile) for the placebo response rate in chronic constipation with different endpoint assessment

	Certainty assessment					No. of patients (studies)	Rate/% (95% CI)	Certainty
Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Subjective improvement								
Randomized trials	Not serious	Serious[a]	Direct	Not serious	None	1,246 (16)	41.40 (31.65–51.15)	⊕⊕⊕○ MODERATE
Composite improvement								
Randomized trials	Not serious	Serious[a]	Direct	Not serious	None	1,545 (9)	20.35 (16.77–23.93)	⊕⊕⊕○ MODERATE
CSBM/CBM								
Randomized trials	Not serious	Serious[a]	Direct	Not serious	None	3,027 (17)	18.31 (13.38–23.23)	⊕⊕⊕○ MODERATE
PAC−SYM scores								
Randomized trials	Not serious	Not serious	Direct	Very serious[b]	None	41 (1)	43.90 (28.71–59.09)	⊕⊕○○ LOW
Improvement in stool consistency								
Randomized trials	serious[c]	Not serious	Direct	Not serious	None	133 (3)	35.12 (27.04–43.2)	⊕⊕⊕○ MODERATE

CI, confidence interval; CSBM/CBM, complete (spontaneous) bowel movement; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; PAC−SYM, Patients Assessment on Constipation Symptoms.
[a]Larger heterogeneity observed.
[b]Study include few patients and have wide CI.
[c]Unclear methods of randomization or allocation concealment in some of studies.

results probably unreliable because of limitation of the number of studies. Another finding is that the placebo response rate decreased a lot with the prolongation of treatment, which lead us to the speculation that the placebo effect may be a short-term effect that weakens with the duration of treatment.

Other studies showed that more possibility to receive active drug can increase the expectation of symptom improvement, as a result, increasing the placebo response (27). This leads to the contradiction with our studies and another meta-analysis of IBS (28), in which patients assigned to placebo at a proportion of approximately 50% had a higher placebo response rate than those significantly less than 50%, though without statistical difference.

The variation of the placebo response rate caused by the factor active treatment may due to patient expectations of the different pharmacological effects they were told. The placebo response rate in RCTs using serotonergic enterokinetic agents as active treatment was higher, although insignificantly, than that of secretagogues, which is consistent with other study (21). It is interesting to recognize that the highest placebo response rate occurs in studies using dietary supplement (fiber, probiotic, and symbiotic) as active treatment. This may give a new idea for combination therapy of dietary supplements and other drugs in clinic practice.

The placebo response rate of RCTs with subjective improvement is 41.40%, which has not been reported elsewhere. This phenomenon is in line with the results of studies in other disease, where the placebo response level is higher when the outcome was the subjective experience of symptom relief assessed by patients themselves (29,30). The less stringent subjective endpoint used to evaluate treatment efficiency in clinical trials for constipated patients mostly applied only 1 single question asked about their subjective feeling about overall symptom relief, making it susceptible to placebo effect. However, what actual helpful on treatment efficiency assessment are those visible and objective facts: increase in CSBM, change in stool consistency, etc. As introduced above, it is the consensus to minimize placebo response in clinical trials (12,13,16). This finding highly indicates that it is essential to reduce the placebo response rate in a clinical trial by avoiding subjective endpoint, and using more stringent outcome assessment to reflect the real effect of new drug, such as improvement in CSBM/CBM and composite improvement.

Publication bias is absent in this meta-analysis for 2 reasons. First, publication bias is not the only reason which can leads to the asymmetry of funnel plot (31–33) and the method developed by Peters et al. (22) gives a way to distinguish the reason that causes funnel plot asymmetry. Trim and fill added 3 "missing" studies in our analysis, and all of them located in the area of $P < 0.01$ (Figure 4b), which indicates that the observed asymmetry probably not caused by publication bias based on Peters' theory. Second, after added 2 moderators (active treatment and endpoint assessment) to adjust the result, funnel plot asymmetry disappeared and the Egger test confirmed it (Figure 4c). These 2 moderators are also the 2 main factors contributing to the great heterogeneity among studies according to meta-regression, which points to the explanation that high heterogeneity among studies causes the asymmetry of funnel plot in this meta-analysis.

This study investigated the pooled placebo response rate and its related factors. And, this is the first systematic review and meta-analysis compared the placebo response rate of constipated

patients among different endpoint assessments used in RCTs so far. Our study gave evidence for further design of clinical trials to reduce the placebo response rate and detect more reliable drug efficacy. The above result can also be applied in clinical practice to enhance the treatment response of patients with CC. Compared with the placebo response rate reported in RCTs, the results obtained in this study can provide a higher level of evidence for the level of placebo response in constipated patients (34,35). Previous articles had discussed the impact of patient characteristics on placebo response (30,36), while our study lacked individual patient data to provide any evidence. Active treatment and endpoint assessment together could explain more than half of the heterogeneity observed in this study. Although with high heterogeneity, the result obtained here is still stable and credible according to sensitivity analysis. In conclusion, we do not recommend subjective endpoint in therapeutic RCTs for chronic constipated patients based on findings in this study. And, the phenomenon of placebo response in patients with CC remains to be investigated.

CONFLICTS OF INTEREST

Guarantor of the article: Tao Bai, MD.

Specific author contributions: Jie Chen, MD, and Xinghuang Liu, MD, contributed equally to this work. T.B. and X.H. developed the main idea of this study. J.C. developed the search strategy. J.C. and X.L. independently finished the selection of studies, data extraction, assessment of the risk of bias, and data synthesis. The disagreements between J.C. and X.L. were arbitrated by T.B. J.C. drafted the original manuscript, which was revised by T.B. All the authors have read and approved the final manuscript.

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Potential competing interests: None to report.

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